Cardiac Troponin Elevation, Cardiovascular Morbidity, and Outcome After Subarachnoid Hemorrhage

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Background—Cardiac troponin I (cTI) release occurs frequently after subarachnoid hemorrhage (SAH) and has been associated with a neurogenic form of myocardial injury. The prognostic significance and clinical impact of these elevations remain poorly defined.

Methods and Results—We studied 253 SAH patients who underwent serial cTI measurements for clinical or ECG signs of potential cardiac injury. These patients were drawn from an inception cohort of 441 subjects enrolled in the Columbia University SAH Outcomes Project between November 1998 and August 2002. Peak cTI levels were divided into quartiles or classified as undetectable. Adverse in-hospital events were prospectively recorded, and outcome at 3 months was assessed with the modified Rankin Scale. Admission predictors of cTI elevation included poor clinical grade, intraventricular hemorrhage, loss of consciousness at ictus, global cerebral edema, and a composite score of physiological derangement (all \( P < 0.01 \)). Peak cTI level was associated with an increased risk of echocardiographic left ventricular dysfunction (odds ratio [OR], 1.3 per quintile; 95% CI, 1.0 to 1.7; \( P = 0.03 \)), pulmonary edema (OR, 2.1 per quintile; 95% CI, 1.6 to 2.7; \( P < 0.001 \)), hypotension requiring pressors (OR, 1.9 per quintile; 95% CI, 1.5 to 2.3; \( P < 0.001 \)), and delayed cerebral ischemia from vasospasm (OR, 1.3 per quintile; 95% CI, 1.07 to 1.7; \( P = 0.01 \)). Peak cTI levels were predictive of death or severe disability at discharge after controlling for age, clinical grade, and aneurysm size (adjusted OR, 1.4 per quintile; 95% CI, 1.1 to 1.9; \( P = 0.02 \)), but this association was no longer significant at 3 months.

Conclusions—cTI elevation after SAH is associated with an increased risk of cardiopulmonary complications, delayed cerebral ischemia, and death or poor functional outcome at discharge. (Circulation. 2005;112:2851-2856.)

Key Words: aneurysm ■ cerebral infarction ■ echocardiography ■ subarachnoid hemorrhage ■ troponin I

Electrocardiographic abnormalities and myocardial enzyme release occur frequently after subarachnoid hemorrhage (SAH) but are widely regarded as epiphenomena that reflect adverse intracranial events without contributing directly to morbidity or mortality.\(^1\)\(^-\)\(^3\) ECG changes such as QT prolongation and repolarization abnormalities occur in 50% to 100% of SAH patients and are not associated with poor outcome.\(^2\)\(^-\)\(^3\) Detectable cardiac troponin I (cTI) release occurs in 20% to 40% of patients, but these elevations are usually small, with the vast majority below the diagnostic threshold for myocardial infarction.\(^4\)\(^-\)\(^5\)

In the most severe form of cardiac injury after SAH, myocardial enzyme release is associated with a syndrome of neurogenic stunned myocardium characterized by reversible left ventricular (LV) systolic dysfunction, cardiogenic shock, and pulmonary edema.\(^6\) Pathologically, this form of myocardial injury is characterized by subendocardial contraction band necrosis, which is thought to result from excessive release of norepinephrine from the cardiac sympathetic nerves.\(^5\)\(^-\)\(^9\) Angiographic obstructive coronary artery disease is not part of the syndrome,\(^10\) and the extent of cTI elevation is generally much smaller than occurs with similar degrees of echocardiographic dysfunction after myocardial infarction.\(^4\)

Although small cohort studies have linked myocardial enzyme release after SAH to impaired LV hemodynamic performance\(^11\) and an increased risk of pulmonary edema,\(^12\) the impact of cTI elevation on in-hospital morbidity and long-term outcome is largely unknown. In this study, we evaluated the prognostic value and clinical significance of acute cTI elevation after SAH.

Methods

Subjects

Between November 1998 and October 2002, 441 consecutively admitted SAH patients were enrolled in the Columbia University...
SAH Outcomes Project. The study was approved by the Institutional Review Board of the hospital, and written informed consent was obtained from the patient or a surrogate in all cases. The diagnosis of SAH was established by CT scan or by xanthochromia of the cerebrospinal fluid if the CT was nondiagnostic. Patients with spontaneous aneurysmal and nonaneurysmal SAH were included in the study. Those with SAH resulting from trauma, AV malformations, or other secondary causes were excluded, as were patients <18 years of age and those admitted >14 days after hemorrhage. All patients were given normal saline at 1 mL · kg⁻¹ · h⁻¹ and supplemental 5% albumin solution to maintain central venous pressure >5 mm Hg, and those with symptomatic vasospasm were given fluids to maintain central venous pressure >8 mm Hg or pulmonary artery diastolic pressure >14 mm Hg and vasopressors (usually phenylephrine, at doses up to 4 µg · kg⁻¹ · min⁻¹) to maintain a systolic blood pressure >200 mm Hg. The clinical management of our patients has otherwise been described in detail previously.13,15

Cardiac Testing
All patients had an ECG on admission, and 253 (62%) had ≥1 cTI measurements. In addition, ECGs obtained from transferring hospitals were reviewed. According to our management protocol,14 cTI was measured in all patients with an abnormal ECG (Q waves, QTc prolongation, ST-segment abnormalities, or T-wave inversion) or clinical signs or symptoms of potential cardiovascular dysfunction (pulmonary edema, hypertension or hypotension [systolic blood pressure >160 or <100 mm Hg, respectively], cardiac dysrhythmia, or chest pain). When the first cTI level was abnormal (>0.3 µg/L in our laboratory), daily serial measurements were obtained as clinically indicated, and a transthoracic echocardiogram was performed. In our laboratory, cTI levels >2.0 µg/L are considered diagnostic of myocardial ischemia. When >1 cTI measurement was obtained on any calendar day, the highest level was analyzed. Echocardiograms were evaluated for LV wall motion abnormalities by a cardiologist who was unaware of the patient’s clinical status.

Admission Clinical and Radiographic Variables
Demographic data, past medical and social histories, and clinical features on admission were obtained through patient and surrogate interviews and medical chart review by a study neurointensivist. Prior cardiac disease was defined as a history of angina, myocardial infarction, arrhythmia, heart failure, or valvular heart disease. The calendar day of SAH onset was referred to as SAH day 0. Details about symptoms at the onset of hemorrhage, admission Glasgow Coma Scale, Hunt-Hess grade (see Table 1), Hijdra SAH CT score, and other clinical and laboratory findings were recorded as described previously.15 To evaluate acute physiological dysfunction, we calculated the SAH Physiological Derangement Score, a previously validated measure of oxygenation, serum bicarbonate, glucose level, and blood pressure abnormalities (0 = best, 8 = worst).15

In-Hospital Complications
At the completion of each patient’s hospitalization, we recorded length of stay and significant complications that had occurred according to prespecified criteria. When the diagnosis of a particular complication was unclear, designations were adjudicated by consensus of the study team after a review of pertinent laboratory and imaging data in a weekly conference. Delayed cerebral ischemia (DCI) resulting from vasospasm was defined as delayed clinical deterioration, cerebral infarction, or both after other possible causes were rigorously excluded.15 Pulmonary edema was defined as the development of ≥2 characteristic clinical findings (pulmonary infiltrates on chest radiography, hypoxemia [Po2/Fio2 <300], and rales). Hypotension was defined as a systolic blood pressure <100 mm Hg treated with vasopressors.

Follow-Up Assessment
Outcome was assessed with the modified Rankin Scale (mRS) at SAH day 14 (or discharge if earlier) and at 3 months by telephone or in-person interview of the patients and informants. Poor outcome was defined as severe functional disability or death (mRS, 4 to 6). When a 3-month outcome assessment was not available, the day 14 mRS score was substituted according to the principle of last observation carried forward. All assessment instruments were administered in the native language (English or Spanish) of the subject or informant.

Statistical Analysis
Statistical analyses were performed with commercially available software (SPSS, version 11). Continuous, normally distributed vari-
Significance was judged by the 3 most consistently identified admission predictors of severity, this relationship was examined after controlling for age, variables. To determine whether the relationship between peak cTI and dichotomous measured. For four percent of the study cohort (n = 81), on day 1 in 36% (n = 92), on day 2 in 11% (n = 28), and on day 3 or later in 29% (n = 72) (Figure 1). In 80% of patients (n = 200), the first cTI measurement was the highest; the median interval between hemorrhage onset and peak cTI was 1.7 days (interquartile range, 1.1 to 4.8 days); no patient had a peak cTI level detected after hospital day 3. Thirty-two percent of tested patients (n = 81) had no detectable cTI; those with elevations were classified as >0 to 0.5 μg/L (n = 46, 18%), >0.5 to 2.0 μg/L (n = 46, 18%), >2.0 to 10.0 μg/L (n = 34, 14%), and >10.0 μg/L (n = 46, 18%). Only 2 of the 172 patients with cTI elevation had normal clinical examination, echocardiogram, and serial ECGs.

Admission clinical and radiographic variables predictive of increased peak cTI levels included higher Hunt-Hess grade, intraventricular hemorrhage or global cerebral edema on admission CT, loss of consciousness at ictus, more severe physiological derangement (higher SAH-Physiological Derangement Score), and an abnormal admission ECG (Table 2). There was no association between peak cTI and age, gender, extent of SAH, aneurysm location, or history of hypertension or cardiac disease.

Cerebral infarction, DCI, and hypotension requiring vasoressors were the most common cardiovascular and cerebrovascular in-hospital complications (Table 2). Quintile of peak cTI level was significantly associated with an significantly increased risk of abnormal LV wall motion on echocardiography, pulmonary edema, hypotension treated with pressors, DCI from vasospasm, and cerebral infarction from any cause (Table 2). With peak cTI levels >0.5 μg/L, the risk of DCI exceeded 50%; with levels >2.0 μg/L, the risk of pulmonary edema exceeded 30%; and with levels >10.0 μg/L, the risk of developing hypotension exceeded 40% (Table 3).

Three-month outcome data were available in 180 patients (71%); in another 50 patients (20%), the day 14 or discharge mRS score was available, so this information was carried forward. Overall, 30% of patients (n = 70) were dead (mRS, 6), 21% (n = 47) were severely disabled (mRS, 4 to 5), 40% (n = 90) were mildly to moderately disabled (mRS, 2 to 4), and 19% (n = 42) had no disability (mRS, 0 to 1) at 3 months (Figure 2). Quintile of cTI elevation was significantly associated with an increased likelihood of death and death or severe disability at 3 months (Table 2). After correction for admission Hunt-Hess grade, age, and aneurysm size, quintile of peak cTI remained associated with death or severe disability at discharge (odds ratio [OR], 1.4 per quintile; 95% CI, 1.1 to 1.9; P = 0.02) but was no longer associated with these outcomes at 3 months (OR 1.2, 95% CI 0.9 to 1.6; P = 0.20). Among those who survived to hospital discharge, quintile of peak cTI was also associated with increased hospital length of stay (mean, 22.9 days; P = 0.01, ANOVA).

To determine the extent to which our findings reflect a neurogenic mechanism of myocardial injury, we repeated all analyses after excluding patients with a known history of heart disease of any type (n = 10). All significant associations identified in the primary analysis retained their significance (data not shown).

Discussion

In this study, we found that cTI measurements after SAH have prognostic significance. Peak cTI levels were predictive of an increased risk of hypotension treated with vasopressors, pulmonary edema, LV systolic dysfunction on echocardiography, and DCI from vasospasm. Peak cTI levels were also associated with an increased risk of death or severe disability at discharge after controlling for other important determinants of outcome. These findings suggest that cTI should be measured routinely in SAH patients who present with ECG
changes or clinical signs of potential cardiovascular dysfunction and support the concept that cardiovascular dysfunction in these patients may contribute directly to poor outcome.

The frequency of cTnI elevation (>0 µg/L) was 68% among the patients we tested and 42% in our SAH population overall. In other studies, the reported frequency of cTnI elevation after SAH been reported as 20% to 40%.5,12 We may have underestimated the true frequency of cTnI elevation after SAH because we did not perform measurements in all patients. However, our overall frequency is at the upper range of what has been previously reported, and cardiovascular complications were no more frequent in the patients that we did not test than in those with undetectable cTnI levels (Table 3). This suggests that our criteria for cTnI screening (ECG abnormality, clinical symptoms or signs of cardiovascular dysfunction, or a history of heart disease) probably captured most SAH patients with cTnI elevations.

The median interval between SAH onset and peak cTnI in our study was 1.7 days, a time course similar to that of ischemic myocardial injury related to coronary artery disease. In 80% of patients, the first cTnI measurement was the highest. We observed a small increase in mean cTnI levels on SAH day 3 in our study population, which most likely reflects additional perioperative cardiac injury in some of our patients. From these observations, it seems reasonable to measure cTnI serially for the first 3 days after SAH.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency, %</th>
<th>Association With cTnI Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunt-Hess grade 4 or 5</td>
<td>37</td>
<td>1.7 (1.4–2.0)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>55</td>
<td>1.3 (1.05–1.6)</td>
</tr>
<tr>
<td>Loss of consciousness at ictus</td>
<td>47</td>
<td>2.0 (1.6–2.5)</td>
</tr>
<tr>
<td>Global cerebral edema</td>
<td>34</td>
<td>1.8 (1.4–2.3)</td>
</tr>
<tr>
<td>SAH physiological derangement score &gt;2†</td>
<td>38</td>
<td>1.6 (1.3–1.9)</td>
</tr>
<tr>
<td>Abnormal ECG‡</td>
<td>69</td>
<td>1.9 (1.3–2.7)</td>
</tr>
<tr>
<td><strong>In-hospital complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiographic LV systolic dysfunction</td>
<td>22</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>17</td>
<td>1.9 (1.4–2.4)</td>
</tr>
<tr>
<td>Hypotension treated with vasopressors</td>
<td>25</td>
<td>1.8 (1.5–2.2)</td>
</tr>
<tr>
<td>Delayed cerebral ischemia from vasospasm</td>
<td>41</td>
<td>1.5 (1.2–1.8)</td>
</tr>
<tr>
<td>Cerebral infarction from any cause</td>
<td>39</td>
<td>1.2 (1.1–1.5)</td>
</tr>
<tr>
<td>Death or severe disability (mRS 4–6)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At discharge</td>
<td>69</td>
<td>1.9 (1.4–2.4)</td>
</tr>
<tr>
<td>At 3 mo</td>
<td>51</td>
<td>1.7 (1.4–2.1)</td>
</tr>
</tbody>
</table>

*Frequency refers to the percentage of the 253 study patients affected by each variable. ORs refer to strength of association per quintile of peak cTnI level (undetectable, >0–0.5, >0.5–2.0, >2–10.0, and >10.0 µg/L).
†Summarizes abnormalities of oxygenation, mean arterial blood pressure, and serum glucose and bicarbonate levels (0=best, 8=worst).
‡Q wave, QTc prolongation (>0.4 ms), T-wave inversion, or ST-T–segment abnormality.
§Available in 230 patients; in 50 patients, the day 14 or discharge mRS score was used.

### TABLE 3. In-Hospital Complications According to Peak cTnI level

<table>
<thead>
<tr>
<th>Peak cTnI Level, µg/L</th>
<th>Abnormal ECG, n (%)</th>
<th>LV Wall Motion Abnormality, n (%)</th>
<th>Pulmonary Edema, n (%)</th>
<th>Hypotension, n (%)</th>
<th>DCI, n (%)</th>
<th>Cerebral Infarction, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not tested</td>
<td>188</td>
<td>80 (43)</td>
<td>6 (3)</td>
<td>7 (4)</td>
<td>24 (12)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Undetectable</td>
<td>81</td>
<td>34 (42)</td>
<td>10 (12)</td>
<td>2 (2)</td>
<td>8 (10)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>&gt;0–0.5</td>
<td>46</td>
<td>35 (76)</td>
<td>5 (11)</td>
<td>5 (11)</td>
<td>11 (24)</td>
<td>17 (37)</td>
</tr>
<tr>
<td>&gt;0.5–2.0</td>
<td>46</td>
<td>37 (80)</td>
<td>3 (7)</td>
<td>5 (11)</td>
<td>13 (28)</td>
<td>23 (50)</td>
</tr>
<tr>
<td>&gt;2.0–10.0</td>
<td>34</td>
<td>27 (79)</td>
<td>11 (32)</td>
<td>12 (35)</td>
<td>10 (29)</td>
<td>18 (53)</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>46</td>
<td>41 (89)</td>
<td>26 (63)</td>
<td>18 (39)</td>
<td>21 (46)</td>
<td>25 (54)</td>
</tr>
</tbody>
</table>

Patients who were not tested for cTnI are shown for comparison but were not included in the primary analysis.
important implications for management. Even cTII elevations <0.5 µg/L were associated with an increased risk of hypotension, pulmonary edema, and DCI compared with undetectable levels, whereas elevations >10 g/L reflected significant cardiac injury, with a likelihood of abnormal wall motion on echocardiography of ~60% and a risk of pulmonary edema or hypotension >40% (Table 3). The increased risk of DCI associated with cTII elevation may reflect impaired LV contractility and hemodynamic performance, which has been associated with symptomatic vasospasm after SAH. Elevated creatine kinase-MB after SAH has been associated with reduced stroke volume and cardiac index and increased systemic vascular resistance in a dose-response fashion; when LV dysfunction is present on echocardiography, these abnormalities become even more pronounced.11

Peak cTII level was independently associated with an increased risk of death or severe disability in our study at discharge, but this association was no longer significant at 3 months. A similar association between minor cTII elevations and mortality has also been described in patients with acute coronary syndromes.10 Acute cTII elevation >2.0 µg/L after SAH should trigger a screening echocardiogram and may be useful for identifying patients who might benefit from invasive hemodynamic monitoring during surgery or during the postoperative period, when hypertensive hypervolemic therapy is commonly administered.

Several potential weaknesses of our study deserve mention. We did not obtain cTII measurements in all SAH patients, did not perform cTII measurements serially according to a prospective protocol, and did not obtain an echocardiogram in all patients with a cTII elevation. Therefore, the true frequency of elevated cTII after SAH cannot be ascertained from these data. We do not have data on the relationship between cTII level and the duration of LV dysfunction after SAH. Approximately 25% of the patients in our study had their first cTII measurement after SAH day 3, which means that we may not have detected important elevations in some of our patients. We also did not exclude patients with known coronary artery disease, which means that both neurogenic and in some patients ischemic myocardial injury occurred in our patients. We dealt with this limitation by repeating our analysis after excluding these patients and obtained similar results. We do not have data on the timing and relative severity of the cardiovascular and neurological complications that occurred during hospitalization. Abnormal echocardiograms were not routinely repeated; thus, we have no information about the relationship between persistent LV dysfunction, cardiovascular morbidity, and outcome. Finally, we had incomplete follow-up data in slightly <10% of out study cohort. Advantages of this study compared with prior investigations of cTII elevation after SAH include the large sample size and our use of prospective in-hospital and outcome data collection.

In summary, our findings indicate that small cTII elevations after SAH have important prognostic significance, particularly with regard to the risk of cardiovascular complications and DCI. Further studies are needed to confirm these findings and to test the utility of intensive care management strategies based on cTII risk stratification.
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References
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